EXHIBIT G

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Tapas Mukhopadhyay, *et al.*

Serial No.: 10/043,877

Filed: January 9, 2002

For: ANTIHELMINTHIC DRUGS AS A TREATMENT FOR HYPERPROLIFERATIVE DISEASES

Group Art Unit: 1642

Examiner: B. J. Fetterolf

Atty. Dkt. No.: INRP:095US

DECLARATION OF TAPAS MUKHOPADHYAY, SUNIL CHADA, ABNER MHASHILKAR, AND JACK A. ROTH UNDER 37 C.F.R. §1.131

We, Tapas Mukhopadhyay, Sunil Chada, Abner Mhashilkar, and Jack A. Roth, hereby declare as follows:

1. We are the joint inventors of the subject matter claimed in the above-referenced patent application, U.S.S.N. 10/043,887, filed January 9. 2002.

2. We are submitting this declaration to set forth facts demonstrating that the invention as reflected in the claims of the above-referenced patent application was reduced to practice prior to January 14, 2000, the PCT filing date of Davis (WO00/41669).

3. Attached as Exhibit 1 is Davis (WO00/41669).

4. Submitted as Exhibit 2 to this declaration is a copy of a draft manuscript of our experiments and results, entitled "Potent Induction of Apoptosis by Anthelmintics in Human Lung Cancer Cells: Involvement of Wild-Type p53 and p21 Kinase Inhibitor," which was prepared prior to January 14, 2000.

5. Reduction to practice is shown by a description of our experiments and results in our draft manuscript (Exhibit 2). This manuscript details our studies pertaining to the effect of benzimidazoles, including fenbendazole and mebendazole, on the regulation of apoptosis in human lung cancer cells. See Exhibit 2, summary, page 2. We studied the *in vitro* effect of fendendazole and mebendazole on human lung cancer cell lines, and found that these drugs dramatically inhibited the growth of lung cancer cells in culture. See Exhibit 2, pages 2 and 9-10, FIG. 1. Both febendazole and mebendazole showed an apoptotic effect on H460 cancer cells. Exhibit 2, page 9-10, FIG. 1. Western blot analysis using specific antibodies against Bcl-2, Bcl-xl, Bax, RB, cdc2, Cdk2, Cyclin A, Cyclin D and p53 demonstrated that benzimidazole treatment resulted in a dose and time dependent nuclear accumulation of wild-type p53, and no alteration in levels of any of the other proteins. Exhibit 2, pages 2, 9-10, FIG. 2, FIG. 3. The kinetics of nuclear accumulation correlated with the induction of apoptotic cell death. Exhibit 2, pages 2 and 10, FIGS. 4-6.

6. The effect of benzimidazole was further assessed on a number of human cell lines. We found that only the cell lines containing the wild-type p53 were highly sensitive to growth inhibition and apoptosis after benzimidazole treatment. Exhibit 2, pages 2 and 11-13, FIGS. 7-8, Table I, and Table II. In contrast, cell lines carrying mutated p53 were less sensitive to the cytotoxic effect of the benzimidazoles. Exhibit 2, pages 2 and 11-13, FIGS. 7-8, Table I, and Table II. Restoration of wild-type p53 function made tumor cells more sensitive to benzimidazole-induced apoptosis. Exhibit 2, page 2 and 12-13, FIG. 8. Our findings indicated that benzimidazoles selectively induce apoptosis in human NSCLC cells, strongly suggesting that a p53 dependent mechanism contributes to the cytotoxicity of benzimidazoles in human cancer cells.

7. All work disclosed in the invention disclosure form was conducted in the United States of America.

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9. Furthermore, we have reviewed WO00/41669 (Davis, Exhibit 1) and the Office Action dated June 28, 2004. Davis fails to disclose the invention set forth in the referenced patent application because it fails to demonstrate a cytotoxic effect of benzimidazoles against cells of a hyperproliferative lesion, such as a tumor. Rather, Davis purports to disclose use of certain 5(6)-substituted benzimidazole-2-carbamates as agents that can damage blood vessels. However, no data demonstrating damage to vasculature is provided. Instead, Davis performed an experiment (page 13, line 1 through page 14, line 4) in CaNT tumor-bearing mice wherein the mice were injected with various compounds intraperitoneally, and then were injected with a fluorescent dye 6 or 24 hr later. One minute later, the animals were killed and tumors evaluated under UV illumination. Blood vessels were identified by fluorescent outlines and vascular volume was said to be quantified using the method of Chalkley, 1943 (J. Natl. Cancer Inst., 4:47-53, 1943; Exhibit 3). However, the "quantitative morphologic tissue analysis" set forth in Chalkley was not contemplated for use in measuring vascular volume. Rather, Chalkley describes a method for evaluating ratios of nucleocytoplasmic volumes or comparing volume ratios of active versus inactive glands. Therefore, it is clear that the methods disclosed in Chalkley are not a validated surrogate assay for vascular volume, and as such, the data presented in Davis is difficult to accurately interpret.

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follow that tumor cell death due to apoptosis will result. For instance, tumor cell death may be by necrosis due to lack of nutrients and oxygen.

14. Furthermore, recent clinical studies have failed to demonstrate significant patient benefit with anti-angiogenic agents, such as thalidomide and endostatin. Davis et al., (Clin. Cancer Res. 10:33-42, 2004; Exhibit 5) recently showed that endostatin can elicit anti-angiogenic effects in human tumors, however the reduced vascularization did not correlate with induction of apoptosis in tumor cells and did not result in tumor growth reduction. Similar lack of efficacy of endostatin was found in an independent study (Thomas *et al.*, J Clin Oncol. 21:223-31, 2003; Exhibit 6), and was also observed in trials with thalidomide (Thomas *et al.*, Br J Haematol. 123:436-41, 2003; Exhibit 7).

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11/02/04 Date	Sunil Chada
Date	Abner Mhashilkar
Date	Jack A. Roth

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